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10/617,568	07/11/2003	Kai W. Wucherpfennig	DFN-044	3949

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/617,568	WUCHERPFENNIG ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2006 and 27 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *19-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/10/05,4/11/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's responses filed 8/9/06 and 11/27/06 are acknowledged and have been entered.

2. Applicant's election without traverse of Group I (claims 1-18), and species of SEQ ID NO: 36 as the spaceholder molecule and effector component that is biotin in Applicant's responses filed 8/9/06 and 11/27/06 is acknowledged.

Claims 1-10 and 13-18 read on the elected species and are presently being examined..

Accordingly, claims 11 and 12 (non-elected species of Group I) and claims 19-50 (non-elected groups II and III) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

3. The use of the trademarks PLURONIC and FICOLL have been noted in this application on page 34 at line 17 and on page 43 at line 19, respectively. They should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-10 and 13-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed MHC class II compound comprising at least a portion of the α and β chains of MHC class II such that they form a peptide binding groove, a spaceholder molecule, including that recited in the dependent claims, and an effector component linked to the MHC class II component, and including those recited in the dependent claims.

The instant claims encompass an MHC class II compound comprising any spaceholder molecule of any sequence, and not necessarily a CLIP peptide or substitution variant thereof capable of binding in the peptide binding groove, and including the spaceholder molecule that *has*, *i.e.,* comprises, the poly-Ala peptide recited in instant claim 10. There is insufficient disclosure in the specification on such a compound.

The specification discloses that "a spaceholder molecule is a peptide that occupies the peptide binding site during biosynthesis and purification, thereby preventing the binding of irrelevant peptides as well as aggregation of the MHC protein." The specification further discloses that examples of spaceholder molecules include SEQ ID NO: 1-5 and 36, the latter having the sequence AAXAAAAAAAAXAA, wherein X is any amino acid residue. The specification discloses that SEQ ID NO: 1 is the CLIP peptide PVSKMRMATPLLMQA, that it can bind in the peptide binding groove of all human and MHC class II molecules, including HLA-DRβ*0101, HLA-DR2a, HLA-DR2b and HLA-DR4. The specification discloses that the CLIP segment of the invariant chain Ii serves to protect the hydrophobic binding groove during assembly, Ii is cleaved following transport to the endosomal/lysosomal peptide-loading compartment and the remaining CLIP peptide is exchanged with other peptides in a reaction catalyzed by HLA-DM. The specification discloses construction of HLA-DR/CLIP tetramers for peptide loading *ex vivo* and identification or expansion of T cell populations. The specification does not disclose if any of SEQ ID NO: 2-5 bind in the peptide binding groove of any MHC class II molecule.

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera, including any lipid or portion thereof. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 4-6 and 11-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

a. Claim 4 is indefinite in the recitation of "wherein said spaceholder molecule binds covalently to said peptide binding groove" because it is not clear what is meant, *i.e.,* if the spaceholder molecule is covalently attached to one of the MHC class II chains, or if there are moieties within the spaceholder molecule that make covalent attachments to the amino acid residue side chains of amino acid residues within or lining the peptide binding groove of the MHC class II molecule.

b. Claim 11 is indefinite in the recitation of "AAMAAAAAAAMAA (SEQ ID NO:2)" because it is not clear what is meant, *i.e,* the recited sequence is 13 amino acid residues in length whereas SEQ ID NO: 2 in the sequence listing filed 7/11/03 is 12 amino acid residues in length.

8. For the purpose of prior art rejections, the filing date of the instant claims 8 and 9 is deemed to be the filing date of the instant application, *i.e.,* 7/11/03, as the parent provisional applications do not support the claimed limitations of the instant application. The limitations "wherein said peptide is about 12-15 amino acid residues" and "wherein said peptide is about 13 amino acid residues" are only disclosed in the instant application.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-9, 13 and 16-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Scott *et al* (J. Exp. Med. 1996, 183: 2087-2095, IDS reference) as evidenced by Kozono *et al* (Nature, 1994, 369: 151-154, IDS reference).

Scott *et al* teach a soluble IA molecule (*i.e.,* the extracellular domains of the α and β chains of an MHC class II) wherein an antigenic peptide sequence, *i.e.,* a spaceholder molecule that binds in the peptide binding groove, is added to the amino terminus of the class II β chain, and wherein the soluble IA molecule comprises leucine zipper peptides linked by a thrombin sensitive cleavage site to the class II chains, *i.e.,* an effector component linked to the MHC class II α chain by a second linker. Scott *et al* teach that the strategy of fusing peptide residues that correspond to the antigenic peptide sequence to the amino terminus of the β chain of class II MHC has been recently described by Kozono *et al* in reference #5.

Evidentiary reference Kozono *et al* (reference #5 of Scott *et al*) teach attaching a peptide by a flexible peptide linker to the amino terminus of the MHC class II β chain and including a thrombin sensitive cleavage site (especially abstract, paragraph spanning columns 1-2 on page 151 and Figure 1A).

With regard to the inclusion of claims 4-6, 8 and 9, while Scott *et al* do not teach the specific affinity of the peptide, Scott *et al* do teach that the peptide is antigenic. Most antigenic peptides have intermediate to high affinity and in some instances are of lower affinity, and MHC class II binding antigenic peptides are about 12-15 amino acid residues minimum as evidenced by both the art reference and the evidentiary reference. Scott *et al* exemplify a 13-mer and a 17-mer antigenic peptide and Kozono *et al* exemplify two 13-mer antigenic peptides.

Therefore the claimed MHC class II compound appears to be the same as the MHC class II compound of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the MHC class II compound of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claims 16-18 are included in this rejection because it is an inherent property of the MHC class II compound that it is encoded by a nucleic acid molecule, and the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

11. Claims 1-5, 7-9 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Kozono *et al* (Nature, 1994, 369: 151-154, IDS reference).

Kozono *et al* teach an MHC class II compound comprising the extracellular domains of the α and β chains of MHC class II, and a peptide attached by a flexible peptide linker to the amino terminus of the MHC class II β chain and including a thrombin sensitive cleavage site, wherein the peptide is a 13-mer peptide that binds well to the binding groove formed by the MHC class II chains, said compound being immobilized by an anti-β chain monoclonal antibody or absorbed to tissue culture plate wells, *i.e.,* the MHC class II component is linked to the effector component (see entire reference, especially abstract, paragraph spanning columns 1-2 on page 151, Figure 1A, Figure 2 and 4 legends).

With regard to the inclusion of claims 4, 5, 8 and 9, while Kozono *et al* do not teach the specific affinity of the peptide, Kozono *et al* do teach that the peptide binds well. Most peptides that bind well have intermediate to high affinity.

Therefore the claimed MHC class II compound appears to be the same as the MHC class II compound of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the MHC class II compound of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

12. Claims 1 and 4-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhong *et al* (J. Exp. Med. 1996, 184: 2061-2066).

Zhong *et al* teach an MHC class II compound comprising the MHC class II α chain and the MHC class II β chain, the β chain linked to the mouse Ii 89-100 invariant chain CLIP peptide via a linker, and the compound further associated with a chemical dye on SDS-PAGE or associated with a radiolabel upon metabolic labeling, *i.e.,* associated with an effector component (see entire reference, especially materials and methods, Figure 1 and Results section).

With regard to the inclusion of claims 4-6, while Zhong *et al* do not teach the specific affinity of the peptide, Zhong *et al* do teach that the complexes containing the covalently attached CLIP peptide do not have a stable conformation on SDS-PAGE analysis, but they are still transported more efficiently than wild-type empty class II dimers, indicating that CLIP peptide can mediate ER to Golgi transport without inducing SDS-stable conformation. By extension, it appears that the CLIP peptide binds with low or intermediate affinity.

Therefore the claimed MHC class II compound appears to be the same as the MHC class II compound of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the MHC class II compound of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1 and 4-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhong *et al* (J. Exp. Med. 1996, 184: 2061-2066) in view of Malcherek *et al* (J. Exp. Med. 1995, 181: 527-536, IDS reference) and DiBrino *et al* (J. Biol. Chem. 1994, 269(51): 32426-32434).

Zhong *et al* teach an MHC class II compound comprising the MHC class II α chain and the MHC class II β chain, the β chain linked to the mouse Ii 89-100 invariant chain CLIP peptide via a linker, and the compound further associated with a chemical dye on SDS-PAGE or associated with a radiolabel upon metabolic labeling, *i.e.,* associated with an effector component. Zhong *et al* teach that the complexes containing the covalently attached CLIP peptide do not have a stable conformation on SDS-PAGE analysis, but they are still transported more efficiently than wild-type empty class II dimers (see entire reference, especially materials and methods, Figure 1 and Results section).

Zhong *et al* do not teach wherein the CLIP peptide is PVSKMRMATPLLMQA, AAMAAAAAAAMAA, AAFAAAAAAAAAA, or AAMAAAAAAAAAA.

Malcherek *et al* teach that the human CLIP peptide amino acid residues 105-117 (SKMRMATPLLMQA) conferred about the same binding as the CLIP 97-120 peptide (LPKPPKPVSKMRMATFLLMQALPM, Figure 2 and the paragraph spanning pages 530-531). Malcherek *et al* further teach that Met107 is the main anchor residues for CLIP to bind different HLA class II alleles and isotypes such as HLA-DR17, -DR1 and -DR4Dw4 (first full paragraph at column 2 on page 532). Malcherek *et al* teach that with regard to CLIP binding to HLA-DR17, Met 107 and Met115 were important, as an Ala scan (*i.e.,* replacing one amino acid in the peptide sequence with Ala, and making a series of peptides, each having only one substitution) of CLIP 106-117 showed that substitution with Ala at these positions led to a decrease of the binding capacity of at least 100- and 10-20 fold, respectively, whereas Phe or Leu substitution for Met115 led to a lesser decrease of the binding capacity and Phe or Leu substitution for Met 107 maintained the parental binding capacity of CLIP or even improved it. Aspartate substitution of these residues completely disrupted binding (paragraph spanning pages 538-529).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have extended the amino terminus of the CLIP 105-117 peptide out sequentially (as well as the carboxy terminus), including making a peptide with the sequence PVSKMRMATPLLMQA (amino acid residues 103-117), in order to determine if binding fully commensurate with the CLIP 97-120 peptide could be obtained, and to have made a construct of the structure taught by Zhong *et al* but using a human HLA class II molecule such as HLA-DR17 taught by Malcherek *et al* that binds the CLIP 105-117 and the CLIP 97-120 peptide, and the extended peptides such as CLIP 103-117.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to study a human HLA and CLIP taught by Malcherek *et al* in the context of cell surface expression as taught by Zhong *et al*.
DiBrino *et al* teach making poly-Ala peptides having residues deemed important for binding to an MHC molecule as well as performing an Ala scan on a peptide to study the contribution of each said residue for binding (especially Table III and column 2 on page 32429).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a peptide with the sequence AA**M**AAAAAA**M**AA, AA**F**AAAAAAAAA, or AA**M**AAAAAAAAAA, *i.e.,* one having the two residues deemed important by Malcherek *et al*, or one having the Met 107 deemed important for binding to HLA-DR4w4, or one with a Phe substituent for Met 107 that improves binding of the parental peptide as taught by Malcherek *et al*, and to have made a construct such as taught by Zhong *et al* for mouse.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to study binding of human HLA class II and human CLIP in the context of cell surface expression as taught by Zhong *et al* for mouse, and because Malcherek *et al* only used Ala scan peptides to assess the contribution of certain residues, said Ala scan peptides have the native amino acid residues at every position except for the scan position where Ala is substituted and DiBrino *et al* teach that making Ala scan peptides as well as poly-Ala peptides is useful for studying the contribution of each residue for binding to an MHC molecule.

15. Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scott *et al* (J. Exp. Med. 1996, 183: 2087-2095, IDS reference) in view of Kozono *et al* (Nature, 1994, 369: 151-154, IDS reference) and Crawford *et al* (Immunity. 1998, 8: 675-682, IDS reference).

Scott *et al* teach a soluble IA molecule (*i.e.,* the extracellular domains of the α and β chains of a murine MHC class II molecule) wherein an antigenic peptide sequence, *i.e.,* a spaceholder molecule that binds in the peptide binding groove, is added to the amino terminus of the class II β chain, and wherein the soluble IA molecule comprises leucine zipper peptides linked by a thrombin sensitive cleavage site to the class II chains, *i.e.,* an effector component linked to the MHC class II α chain by a second linker. Scott *et al* teach that the strategy of fusing peptide residues that correspond to the antigenic peptide sequence to the amino terminus of the β chain of class II MHC has been recently described by Kozono *et al* in reference #5.

Scott *et al* do not teach wherein the effector component is biotin.

Kozono *et al* (reference #5 of Scott *et al*) teach attaching a peptide by a flexible peptide linker to the amino terminus of the MHC class II β chain and including a thrombin sensitive cleavage site (especially abstract, paragraph spanning columns 1-2 on page 151 and Figure 1A).

Crawford *et al* teach multimerization of MHC class II/peptide complexes by including a peptide tag that could be biotinylated, biotinylating the MHC complexes, mixing the MHC class II/peptide complexes with PE/SA (especially materials and methods). Crawford *et al* teach that multimeric soluble MHC class II molecules stably occupied with covalently attached peptides bind with appropriate specificity to T cells, and with higher affinity than the monomeric MHC class II complexes (abstract). Crawford *et al* also teach genetically coupling the peptide of interest to the N terminus of the b chain of class II MHC via a flexible linker so that the peptide is covalently attached to the MHC molecule and stable occupies the peptide binding groove during biosynthesis (last paragraph at column 1 on page 679). Crawford *et al* teach that when MHC/peptide monomers are multimerized, they achieve much higher avidities for the αβTCR on the T cell surface (first paragraph at column 2 on page 675).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have multimerized the complexes taught by Scott *et al*, plus or minus the leucine zipper peptides, using the methodology of Crawford *et al* .

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the avidity of reactivity of the complexes with T cells as taught by Crawford *et al*.

Claims 16-18 are included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

16. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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